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Histopathologic predictors of survival and recurrence in resected ampullary adenocarcinoma: international multicenter cohort study

Alma L. Moekotte, MD¹, Sanne Lof, MD¹, Stijn Van Roessel, MD², Martina Fontana, MD³, Stephan Dreyer, MD^{4,5}, Alaaeldin Shablak, MD, MSc, MRCP⁶, Fabio Casciani, MD³, Vasileios K. Mavroeidis, MD, MSc⁷, Stuart Robinson, MBChB, PhD, FRCS⁸, Khalid Khalil⁹, George Gradinariu, MD¹⁰, Nicholas Mowbray, MD¹¹, Bilal Al-Sarireh, MBChB, FRCS, PhD¹¹, Giuseppe Kito Fusai, MD, MS, FRCS¹⁰, Keith Roberts, MD, PhD⁹, Steve White, MD, MB, ChB, FRCPS, FRCS⁸, Zahir Soonawalla, MS, DNB, FRCS⁷, Nigel. B. Jamieson, MBChB, BSc, FRCS, PhD⁵, Roberto Salvia, MD, PhD³, Marc G. Besselink, MD, PhD², Mohammed Abu Hilal, MD, PhD, FACS, FRCS¹.

1. Department of Surgery, University Hospital of Southampton NHS foundation trust, Southampton, UK.
2. Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, the Netherlands.
3. Department of Surgery, University Hospital of Verona, Verona, Italy.
4. Institute of Cancer Sciences, University of Glasgow, Glasgow, UK.
5. West of Scotland Pancreatic Unit, Glasgow Royal Infirmary, Glasgow, UK.
6. Department of Oncology, University Hospital of Southampton NHS foundation trust, Southampton, UK.
7. Department of Hepatobiliary and Pancreatic Surgery, Oxford University Hospitals NHS Foundation Trust, Oxford, UK.
8. Department of Surgery, Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK.
9. Faculty of medicine, University of Birmingham, Birmingham, UK.
10. Department of Surgery, Royal Free London NHS Foundation Trust, London, UK.
11. Department of Surgery, Morriston Hospital, Swansea, UK.

Corresponding author

Professor Mohammed Abu Hilal, MD PhD FACS FRCS

Department of Hepato-Biliary and Pancreatic Surgery

University Hospital Southampton NHS Foundation Trust

Tremona Road, Southampton SO16 2YD, UK

Tel: +44 7863 354035

Email: abuhilal9@gmail.com

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STRUCTURED ABSTRACT

Objective The aim of the study was to define histopathologic characteristics that independently predict overall survival (OS) and disease-free survival (DFS), in patients who underwent resection of an ampullary adenocarcinoma (AAC) with curative intent.

Summary background data A broad range of survival rates have been described for adenocarcinoma of the ampulla of Vater, presumably due to morphological heterogeneity which is a result of the different epitheliums AAC can arise from (intestinal or pancreaticobiliary). Large series with homogenous patient selection are scarce.

Methods A retrospective multicenter cohort analysis of patients who underwent pancreatoduodenectomy for ampullary adenocarcinoma in nine European tertiary referral centers between February 2006 and December 2017, was performed. Collected data included demographics, histopathologic details, survival and recurrence. OS and DFS analyses were performed using Kaplan-Meier curves and Cox proportional hazard models.

Results Overall, 887 patients were included, with a mean age of 66 ± 10 years. The median OS was 64 months with 1-, 3-, 5- and 10-year OS rates of 89%, 63%, 52% and 37%, respectively. Histopathologic subtype, differentiation grade, lymphovascular invasion, perineural invasion, T-stage, N-stage, resection margin and adjuvant chemotherapy were correlated with OS and DFS. N-stage (HR=3.30 [2.09 – 5.21]), perineural invasion (HR=1.50 [1.01 – 2.23]) and adjuvant chemotherapy (HR=0.69 [0.48 – 0.97]) were independent predictors of OS in multivariable analysis, whereas DFS was only adversely predicted by N-stage (HR=2.65 [1.65 – 4.27]).

Conclusions Independent predictors of OS in resected ampullary cancer were N-stage, perineural invasion and adjuvant chemotherapy. N-stage was the only predictor of DFS. These findings improve predicting survival and recurrence after resection of ampullary adenocarcinoma.

INTRODUCTION

Ampullary adenocarcinoma (AAC) is a rare tumor, accounting for only 0.2% - 0.5% of all gastrointestinal cancers^{1,2} and 7% of all periampullary cancers.³ AAC arises from the ampulla of Vater, at the confluence of the common bile duct and the pancreatic duct into the duodenum. In contrast to other periampullary cancers, AAC often presents at an early stage due to the resulting biliary obstruction.⁴ As a result, AAC is more likely to be resectable at the time of diagnosis and resection rates of AAC are reportedly higher as compared to other periampullary cancers (50% vs 10%).^{5,6} In addition, patients with ampullary cancer tend to have a better prognosis with 5-year survival rates of 30 – 70% after resection.^{1,6–10} This broad range of survival could be explained by the morphological heterogeneity in AAC, which complicates the prediction of individual prognosis and clinical decision making with regard to adjuvant therapy. Because of the anatomical confluence of three structures (duodenum, pancreatic and common bile duct), different histopathologic subtypes have been identified in AAC, based on the epithelium of their origin; intestinal, pancreaticobiliary or a mixed type. It has been suggested that the different histopathologic subtypes have different tumor biology and thus different prognosis.^{11,12} Due to the rarity of the disease, limited data are available on survival in AAC and its corresponding risk factors. Most studies investigating histopathologic predictors of survival in AAC have a small sample size or are based on national registries. The aim of this study is to identify histopathologic predictors of survival and recurrence in a large multicenter cohort of patients who underwent pancreatoduodenectomy for AAC.

METHODS

Patient selection

All consecutive adult patients who underwent pancreatoduodenectomy for AAC between February 2006 and December 2017 in nine tertiary referral centers (seven in the UK, one in the Netherlands and one in Italy) were included. Patients who underwent palliative procedures or local excision of AAC were not included, nor were patients with an R2 resection or distant metastasis. Data were collected on demographics, histopathologic details, treatment, recurrence and survival. The primary outcomes were overall survival (OS) and disease-free survival (DFS).

Work up and treatment

Diagnostic work-up included at least a CT scan of the abdomen, a side view gastroscopy and a biopsy for diagnosis and staging. ERCP, MRI and/or PET scan were performed on indication. Patients underwent either a classic Whipple procedure, pylorus-preserving pancreatoduodenectomy (PPPD) or a total pancreatectomy. Resected specimens were evaluated by certified pathologists and results documented per local protocol.¹³ Patients were staged according to the 7th edition of the American Joint Committee on Cancer (AJCC).¹⁴ Referral for adjuvant chemotherapy was done based on consensus of the local multi-disciplinary team (MDT). The chemotherapy regime was chosen at the discretion of the treating oncologist. No patients received radiotherapy.

Histopathologic subtypes

Classification of intestinal and pancreaticobiliary subtype was based on cytological and architectural features as described by Albores-Saavedra.¹⁵ The intestinal type of AAC arises from the adjacent duodenal mucosa and histologically resembles colonic adenocarcinomas. They are characterized by glands or cribriform nests of cells with central necrosis. The cells are columnar, and usually pseudostratified.¹⁵ Pancreaticobiliary type AAC derives from the terminal pancreatic or biliary

ducts and may arise from adenomas of the Ampulla of Vater. They are characterized by well-formed, angulated tubules that infiltrate the stroma with an associated marked desmoplastic response. The lining cells are cuboidal to columnar and lack pseudo-stratification. They may show clear cell morphology.¹⁵ Mixed type AAC are commonly encountered, they show a combination of intestinal and pancreaticobiliary type morphology. Histopathologic subtype was extracted from the pathology report of the resection specimen. No attempts were made to retrieve paraffin blocks to obtain missing data regarding the subtype, due to the large number of participating centers and the need for close collaboration with local pathologists in every center.

Statistical analysis

Normally distributed variables are reported as means with standard deviation (SD). Non-normally distributed variables are reported as medians with interquartile ranges (IQR). Categorical variables are presented as frequencies and proportions. Categorical data were compared by means of the Chi Square-test, whereas numerical data were compared by the student's *t*-test for normally distributed data and non-normally distributed data by its nonparametric equivalent the Mann-Whitney *U* test. OS was defined as the time in months between surgery and the date of death from any cause, or date of last follow-up. DFS was defined as the time in months between surgery and the date of local recurrence or distant metastasis, or the last date without radiographic or pathological evidence of recurrence. Median OS and DFS were calculated using Kaplan-Meier curves, with subgroups being compared using the log-rank test. Survival rates for 1-, 3-, 5- and 10-year after resection were derived from the life table. Patients who deceased within 30 days after surgery were excluded from survival analyses, as were patients who showed high grade dysplasia on final histology report. Cox proportional hazard models were performed to identify independent predictors of OS and DFS. Univariable analysis was performed for age, sex, adjuvant chemotherapy, resection margin status, T-stage, N-stage, histopathologic subtype, differentiation grade, lymphovascular invasion and perineural invasion. Subsequently, all variables with a *p*-value <0.20 were selected for multivariable analysis. Sub-analysis

was performed to identify predictors of OS for the different histopathologic subtypes. A p -value <0.05 was considered statistically significant. Data were analyzed using SPSS® 24.0 software (SPSS, Chicago, IL, USA).

RESULTS

Patient characteristics

A total of 887 patients were included, with a median number of 91 patients per center (ranging from 63 to 172 cases). Patient demographics and tumor characteristics are reported in table 1. The mean age of the cohort was 66 ± 10 years, 386 (43%) were female and the mean BMI was 26 kg/m^2 . The median tumor size was 20mm (IQR 15 – 30mm), while patients presented most frequently with stage 2B and 3, representing 39% and 26% of the cohort, respectively. A classic Whipple procedure was performed in 252 patients (28.5%), a PPPD in 626 (71%) and 4 patients underwent total pancreatectomy (0.5%). The 30-day mortality of the entire cohort was 4%. Only 21 (3%) patients underwent vascular resection. Overall, 409 (52%) patients received adjuvant chemotherapy.

Histopathologic subtype was documented in 547 patients, of whom 211 had intestinal subtype (39%), 293 pancreaticobiliary subtype (53%) and 43 a mixed subtype (8%). Well, moderately and poorly differentiated adenocarcinoma was seen in 78 (9%), 523 (60%) and 267 (31%) patients, respectively. In 544 patients (61%) lymph node (LN) involvement was present. The number of patients with lymphovascular invasion and perineural invasion was 515 (61%) and 351 (42%), respectively.

Overall survival

At the end of the last follow-up, 480 (58%) patients were still alive with a median follow-up of 39 months (IQR 16 – 64 months). The median OS was 64 months with 1-, 3-, 5- and 10-year OS rates of 89%, 63%, 53% and 37%, respectively. Kaplan-Meier curves for the different histopathologic characteristics are presented in figure 1. Corresponding median OS (in case this was reached) and 1-, 3- and 5-year OS rates for all histopathologic features are demonstrated in supplementary table 1. Using Kaplan-Meier estimates, a worse OS was seen in patients with pancreaticobiliary histopathologic subtype compared to the other subtypes (log-rank $p=0.003$), a higher grade of tumor differentiation

(log-rank $p<0.001$), lymphovascular invasion (log-rank $p<0.001$), perineural invasion (log-rank $p<0.001$), a higher T-stage (log-rank $p<0.001$) and LN involvement (log-rank $p<0.001$).

Table 2 shows uni- and multivariable analyses of risk factors associated with OS. Adjuvant chemotherapy, R1 resection, T3/T4 tumor, LN involvement, pancreaticobiliary histopathologic subtype, poor tumor differentiation, lymphovascular invasion and perineural invasion were all associated with worse OS in the univariable analysis (all $p<0.05$). In the multivariable analysis, both LN involvement (HR=3.30 [2.09 – 5.21, $p<0.001$]) and perineural invasion (HR=1.50 [1.01 – 2.23], $p=0.045$) were associated with worse OS, whereas adjuvant chemotherapy (HR=0.69 [0.48 – 0.97], $p=0.033$) showed to be an independent predictor of an improved OS.

Disease-free survival

Within follow-up, 287 (37%) patients developed recurrence; of whom 88 local recurrence and 176 distant metastasis. In 23 patients, the type of recurrence was not documented. The median DFS was 85 months, with a 1-, 3-, 5- and 10-year DFS of 80%, 57%, 53% and 46%, respectively. As illustrated in supplementary figure 1; a decreased DFS was seen in patients with pancreaticobiliary and mixed histopathologic subtype, a poorer grade of tumor differentiation, presence of lymphovascular invasion, perineural invasion, a higher T-stage and LN involvement (all log-rank $p<0.001$). Corresponding median DFS (if reached) and 1-, 3- and 5-year DFS rates for the previously mentioned histopathologic characteristics are shown in supplementary table 1. Table 3 demonstrates uni- and multivariable analyses of risk factors associated with DFS. Adjuvant chemotherapy, R1 resection, T-stage 3/4, LN involvement, pancreaticobiliary histopathologic subtype, poor tumor differentiation, lymphovascular invasion and perineural invasion were all associated with worse DFS in univariable analysis (all $p<0.05$). Lymph node involvement (HR=2.65 [1.65 – 4.27] $p<0.001$) was the only independent negative predictor of DFS in multivariable analysis. Margin status (R1) did not reach statistical significance but showed a trend towards a worse DFS (HR=1.41 [0.97 – 2.05] $p=0.069$).

Overall survival stratified by histopathologic subtype

The median OS of patients with intestinal subtype was not reached, with estimated 1-, 3-, 5- and 10-year OS rates being 91%, 73%, 60% and 55%, respectively. Table 4 shows uni- and multivariable analyses of risk factors associated with OS in intestinal subtype. R1 resection, a higher T-stage, LN involvement, lymphovascular invasion and perineural invasion were all associated with a worse OS in univariable analysis (all $p < 0.05$). LN involvement was the only independent predictor in multivariable analysis (HR=4.70 [1.98 – 11.14]). Overall, 70 (38%) patients with intestinal subtype received adjuvant chemotherapy.

The median OS of patients with pancreaticobiliary subtype was 47 months, with estimated 1-, 3-, 5- and 10-year OS rates of 87%, 54%, 47% and 32%, respectively. Table 5 shows uni- and multivariable analyses of risk factors associated with OS in pancreaticobiliary type AAC. R1 resection, LN involvement, lymphovascular invasion and perineural invasion were associated with a worse OS in univariable analysis (all $p < 0.05$). LN involvement (HR=2.97 [1.65 – 5.34]) was an independent negative predictor of OS in pancreaticobiliary type. Adjuvant chemotherapy (HR=0.61 [0.40 – 0.93]) independently predicted an improved OS in pancreaticobiliary subtype. In total, 160 (60%) patients with pancreaticobiliary received adjuvant chemotherapy.

DISCUSSION

This represents the largest multicenter study on resected AAC to date. All histopathologic characteristics investigated in this study (histopathologic subtype, differentiation grade, T-stage, N-stage, lymphovascular invasion, perineural invasion) were highly correlated with both OS and DFS. The 5-year OS varied from 33% to 75% depending on the histopathologic characteristic. These findings support the hypothesis that there is great morphological heterogeneity in AAC, which influences outcome. LN involvement and perineural invasion were independent predictors of a worse OS in multivariable analysis. Conversely, adjuvant chemotherapy showed a favorable effect on OS. DFS was independently adversely predicted by LN involvement alone.

Multiple unfavorable histopathologic predictors for resected AAC have been described in the literature.^{11,12,16–19} However, these studies are not comparable with our study. First, all but one study were monocenter studies. Second, most studies have only included few characteristics, leaving out characteristics that might have been associated with oncological outcomes. Third, one study also included patients who underwent transduodenal local excision.¹¹ Furthermore, most studies report outcomes of patients who were treated in the last 2 decades of the 20th century; unsurprisingly they reported higher postoperative mortality rates (5 – 10%) after pancreatoduodenectomy than the more recently published 2-5% mortality, which is comparable to the 4% mortality in the current study.^{20,21} Doepker and colleagues described tumor differentiation and pancreaticobiliary subtype as independent predictors of OS in a monocenter cohort of 106 patients with resected AAC. LN involvement showed a trend towards decreased OS in their study.²² However, adjuvant chemotherapy and T-stage were not included in their analysis; this could have influenced the outcome, as these two variables were associated with OS in our cohort. In line with our results, Duffy and colleagues have reported perineural invasion as an independent predictor of OS in a monocenter cohort of 55 patients with resected AAC.¹⁶ Similar findings were reported by Lazaryan and colleagues in a cohort of 72 patients.¹⁸ Furthermore, Qiao and colleagues reported LN involvement as an independent predictor of OS in a cohort of 102 patients with resected AAC.¹⁷ Chang and colleagues investigated histopathologic

features and protein expression (CDX2 and MUC1) and outcome in three different cohorts; LN involvement was an independent predictor for OS in all three cohorts, pancreaticobiliary subtype in two of the three cohorts.¹² Carter and colleagues reported perineural invasion to be an independent predictor of OS in their cohort of 107 patients, as well as lymphovascular invasion and pancreaticobiliary subtype.¹¹

The 5-year DFS survival in the current study was 53%, highly similar as reported by others (55-58%).^{19,23} Conversely, Lazaryan and colleagues reported a higher 5-year DFS of 73% in a cohort of 72 patients.¹⁸ This can be explained by their lower overall TNM stage and the lower proportion of LN involvement compared to our cohort. Doecker and colleagues described a lower 5-year DFS of 36% in a cohort of 106 patients.²² The smaller sample size of previously mentioned monocenter studies make them less generalizable than our study. The sole independent predictor that adversely affected DFS in our cohort was LN involvement. Unfavorable predictors of DFS in the previously mentioned reports were LN involvement,^{19,22,23} pancreaticobiliary subtype,^{22,23} perineural invasion,¹⁸ T-stage²³ and differentiation grade.²³ However, one or more variables that were associated with DFS in our study were missing in in these reports, which might have caused the difference in outcome.

Although AAC is a rare tumor, it does account for a fairly large proportion (20 – 46%) of all pancreatoduodenectomies performed for cancer, likely because of its relatively early presentation.^{3,17,24} Due to this substantial proportion, predicting prognosis as well as knowing the effectiveness of adjuvant chemotherapy is of clear clinical relevance. Adjuvant chemotherapy was an independent predictor of improved OS in this study. No clear guidelines or protocols exist on which patients should receive adjuvant chemotherapy for ampullary cancer. Therefore, the decision to give adjuvant chemotherapy was based on the discretion of the treating oncologist. Patients who received adjuvant chemotherapy were younger, but more often presented with unfavorable features (larger tumor size, more advanced AJCC 7 stage, LN involvement, R1 resection, pancreaticobiliary subtype, perineural invasion and lymphovascular invasion) compared to patients who did not receive adjuvant chemotherapy. It is likely that the decision to give adjuvant chemotherapy was (at least partially) based

on these characteristics. The role of adjuvant chemotherapy for periampullary cancers has been investigated in the international EPSAC-3 trial. In this study 434 patients with periampullary cancer from 100 centers in 18 countries were randomized to one of three arms: observation, 5-FU/leucovorin or gemcitabine. Although no difference was seen in OS between the groups,²⁵ this study demonstrated a trend toward improving overall survival favoring the chemotherapy group versus observation (median OS 43 months vs 35 months respectively; $p=0.25$). Interestingly, a sub-group analysis revealed that patients with AAC treated with gemcitabine had an improved OS compared with the other 2 groups (median OS 70.8 months vs 40.6 months vs 57.8 months for gemcitabine, observation and 5-FU/leucovorin, respectively). Subsequently, the ESPAC-3 v2 trial reported a survival benefit favoring adjuvant chemotherapy versus observation in patients with R0 resection (median OS 58.4 months vs 45.1 months for chemotherapy vs observation, $p=0.057$).²⁶ In addition, several retrospective studies have reported an increased survival in patients receiving adjuvant chemotherapy after resection of AAC.^{27–29} Finally, an ongoing international multicenter study (ESPAC-4) is assessing the effectiveness of the doublet gemcitabine and capecitabine adjuvant chemotherapy compared to gemcitabine alone in periampullary cancer.

Sensitivity analysis performed in this study, revealed adjuvant chemotherapy was only an independent predictor of increased OS in the 293 patients with pancreaticobiliary subtype (HR=0.61 [0.40 – 0.93, $p=0.023$]) but not for the 211 patients with intestinal subtype (HR=1.06 [0.57 – 1.95], $p=0.861$). Importantly, this finding illustrates that patients with pancreaticobiliary subtype might benefit from adjuvant chemotherapy. To date, no other studies have demonstrated a difference in effect of adjuvant chemotherapy between the different histopathologic subtypes. Interestingly, histopathologic subtype was not documented in 340 of the 887 histopathology reports. Suggesting that many pathologists do not consider it. The authors believe that reporting the histopathologic subtype is of high clinical relevance as it not only predicts prognosis but also selects patients who are likely to benefit from adjuvant chemotherapy. Adjuvant chemotherapy should therefore be offered to all patients with pancreaticobiliary subtype.

This study has several limitations. First, it was a retrospective study with a risk of information bias. However, because the characteristics studied were pathology findings and the primary study outcome was survival, it seems that information bias may not have played a relevant role. Second, data on the chemotherapy regimens were not collected. Although, we know the most commonly used regime in the UK is gemcitabine, no clear guidelines exist on adjuvant therapy in AAC. The regime given, was based on the discretion of the treating oncologist, therefore, regimes could have varied between centers. Third, the OS is much longer than the follow-up. The main strength of our study is that, to the best of our knowledge, this is the largest cohort of resected AAC described in the literature to date.

In conclusion, unfavorable predictors of OS were LN involvement and perineural invasion, whereas adjuvant chemotherapy independently predicted improved OS. DFS was independently predicted by LN involvement. Sub-analysis of the histopathologic subtypes revealed that patients with the pancreaticobiliary subtype benefit from adjuvant chemotherapy in terms of survival.

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